



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification:</b> <b>C12Q 1/68, A01N 43/04,</b> <b>C07H 19/00, C07H 21/00,</b> <b>C07H 21/02, C07H 21/04</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 99/66063</b> <b>(43) International Publication Date:</b> 23 December 1999 (23.12.1999)
<b>(21) International Application Number:</b> PCT/US99/13565 <b>(22) International Filing Date:</b> 16 June 1999 (16.06.1999) <b>(30) Priority Data:</b> 09/098,166 16 June 1998 (16.06.1998) US 09/275,505 24 March 1999 (24.03.1999) US <b>(60) Parent Application or Grant</b> ISIS PHARMACEUTICALS, INC. [/]; (). MANOHARAN, Muthiah [/]; (). BHAT, Balkrishn [/]; (). COOK, Phillip, Dan [/]; (). GUZAEV, Andrei, P. [/]; (). MANOHARAN, Muthiah [/]; (). BHAT, Balkrishn [/]; (). COOK, Phillip, Dan [/]; (). GUZAEV, Andrei, P. [/]; (). CALDWELL, John, W. ; ().		<b>Published</b>
<b>(54) Title: NUCLEOSIDIC AND NON-NUCLEOSIDIC FOLATE CONJUGATES</b> <b>(54) Titre: CONJUGUES DE FOLATES NUCLEOSIDIQUES ET NON NUCLEOSIDIQUES</b>  <b>(57) Abstract</b> <p>The invention is directed to mononucleosides and oligonucleotides that are conjugated to folic acid, related folates, antifolates and analogs thereof, and to non-nucleosidic folate conjugates. Methods for the preparation of nucleosidic and non-nucleosidic conjugates are also disclosed.</p> <b>(57) Abrégé</b> <p>L'invention porte sur des conjugués de folates oligonucléotidiques, les folates étant conjugués à un plusieurs sites sur un oligonucléotide comprenant les sites de liaison nucléobase et internucléotide 2', 3', 5'. Le folate peut être lié par le carboxylate 'alpha' ou 'gamma', éventuellement par un groupe de liaison. L'invention porte également sur des procédés de synthèse régiospécifiques des conjugués, et sur des séquences de liaison nucléosidiques et non nucléosidiques conjuguées à l'acide folique et aux folates correspondants.</p>		

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(51) International Patent Classification <sup>6</sup> : <b>C12Q 1/68, C07H 19/00, 21/00, 21/02, 21/04, A01N 43/04</b>		<b>A3</b>	(11) International Publication Number: <b>WO 99/66063</b> (43) International Publication Date: 23 December 1999 (23.12.99)
(21) International Application Number: <b>PCT/US99/13565</b> (22) International Filing Date: 16 June 1999 (16.06.99) (30) Priority Data: 09/098,166 16 June 1998 (16.06.98) US 09/275,505 24 March 1999 (24.03.99) US (71) Applicant (for all designated States except US): <b>ISIS PHARMACEUTICALS, INC. [US/US]; 2292 Faraday Avenue, Carlsbad, CA 92008 (US).</b> (72) Inventors; and (75) Inventors/Applicants (for US only): <b>MANOHARAN, Muthiah [US/US]; 7634 Reposado Drive, Carlsbad, CA 92009 (US). BHAT, Balkrishen [IN/US]; 911 Rosemary Avenue, Carlsbad, CA 92009 (US). COOK, Phillip, Dan [US/US]; 1155 La Casa, Lake San Marcos, CA 92069 (US). GUZAEV, Andrei, P. [RU/US]; 7702 Caminito Leon, Carlsbad, CA 92009 (US).</b> (74) Agents: <b>CALDWELL, John, W. et al.; Woodcock Washburn Kurtz Mackiewicz &amp; Norris LLP, 46th floor, One Liberty Place, Philadelphia, PA 19103 (US).</b>		(81) Designated States: <b>AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.</b> ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  Published With international search report. (88) Date of publication of the international search report: 20 April 2000 (20.04.00)	
(54) Title: <b>NUCLEOSIDIC AND NON-NUCLEOSIDIC FOLATE CONJUGATES</b>			
(57) Abstract  The invention is directed to mononucleosides and oligonucleotides that are conjugated to folic acid, related folates, antifolates and analogs thereof, and to non-nucleosidic folate conjugates. Methods for the preparation of nucleosidic and non-nucleosidic conjugates are also disclosed.			

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/13565

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C12Q 1/68; C07H 19/00, 21/00, 21/02, 21/04; A01N 43/04

US CL : 435/6; 536/22.1, 23.1, 24.3, 25.3; 514/44.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6; 536/22.1, 23.1, 24.3, 25.3; 514/44.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN

search terms: oligonucleotide, antisense, folic acid, non-nucleosidic, conjugates, folate...

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HABUS et al. A Mild and Efficient Solid-Support Synthesis of Novel Oligonucleotide Conjugates. Bioconjugate Chem. April 1998, Vol 9, No. 2, pages 283-291, see entire document.	1-6, 13-20 and 94-100

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* I* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A* document defining the general state of the art which is not considered to be of particular relevance	* X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* B* earlier document published on or after the international filing date	* Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* A* document member of the same patent family
* O* document referring to an oral disclosure, use, exhibition or other means	
* P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 NOVEMBER 1999

Date of mailing of the international search report

23 DEC 1999

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/13565

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all-searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-6, 13-20, and 94-100

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/13565

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-6, 13-20, and 94-100, drawn to a first compound and a method for preparing the same.

Group II, claim(s) 7-12, 23-30, 34, 36-42, 45-61, 65-72, and 93, drawn to a second compound where  $X_3$  is compound XI and a method of making the same.

Group III, claim(s) 7-12, 23-27, 29-33, 35-42, 45-81, drawn to a third compound where  $X_3$  is compound XII and a method of making the same.

Group IV, claim(s) 21 and 23, drawn to 4th compound and method of making.

Group V, claim(s) 22 and 23, drawn to a 5th compound and method of making the same.

Group VI, claim(s) 43 and 44, drawn to a method of making a folic acid derivative.

Group VII, claim(s) 82-86, drawn to 7th compound where  $X_3$  is compound XI.

Group VIII, claim(s) 82, 87-90, drawn to a 8th compound where  $X_3$  is compound XII.

Group IX, claim(s) 91, drawn to a 9th compound.

Group X, claim(s) 92, drawn to 10th compound.

The inventions listed as Groups I-X do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the 10 inventions relates to 10 different special technical features and method of making them.